

*RATIO SIZE AND COCAINE CONCENTRATION
EFFECTS ON ORAL COCAINE-REINFORCED BEHAVIOR*

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Monkeys were given a choice between cocaine solutions and water under concurrent fixed-ratio reinforcement schedules. The operant response was spout contact. Six rhesus monkeys served as subjects. The cocaine concentration was varied from 0.0125 to 0.8 mg/ml, and the fixed-ratio value was varied from 8 to 128. Cocaine maintained higher response rates than did water over a wide range of conditions. Response rate and number of cocaine deliveries per session were inverted U-shaped functions of concentration. These functions were shifted to the right as the fixed ratio was increased. The number of cocaine deliveries was more persistent as fixed-ratio value was increased when the unit dose was larger rather than smaller. Cocaine consumption was analyzed as a function of unit price (fixed-ratio value divided by cocaine concentration), and unit price accounted for between 77% and 92% of the variance in cocaine consumption for individual monkeys. The current data support the claim that a drug's reinforcing effects increase directly with dose and underscore the need to gather parametric data when examining the effects of experimental manipulations on a drug-reinforced baseline.

Key words: oral cocaine self-administration, relative reinforcing effects, behavioral momentum, behavioral economics, fixed-ratio schedules, spout contact, rhesus monkeys

Drug-reinforced behavior can be altered following changes in environmental, behavioral, or physiological variables (Carroll, Carmona, & May, 1991; Glowa et al., 1995; Spear & Katz, 1991). Data from animals self-administering drugs are often used to infer relations between an independent variable that is manipulated and the drug's reinforcing effects. To make such inferences, it is necessary to understand the relation between a drug's reinforcing effects and the dependent measures used to index the reinforcing effects. Clear explication of this relation has been difficult partly because of the lack of parametric data.

Response rate traditionally has been used to assess response strength, response probability, and reinforcer effectiveness. A significant problem with using absolute response rate as an index of reinforcer effectiveness is

that response rate is multidetermined (Zeiler, 1977). That is, the ability of the reinforcing stimulus to maintain behavior is only one of multiple variables that affect response rate. When drugs are used as reinforcers, response rate is typically an inverted U-shaped function of drug dose (Woolverton & Nader, 1990). The ascending limb can be interpreted to reflect increasing reinforcing effects of drugs (Katz, 1989; Skjoldager, Winger, & Woods, 1991). Researchers have disagreed about the reasons for the descending limb, but the reduction in responding is most likely not due to a decrease in reinforcing effects.

Progressive-ratio methods, in which the number of responses required for reinforcer delivery is gradually increased within a session or across days (e.g., Griffiths, Findley, Brady, Dolan-Gutcher, & Robinson, 1975; Hodos, 1961), have also been used to assess reinforcer effectiveness. The *break point* is the largest number of responses emitted (or ratios completed) during the session. The relation between break point and drug dose is reported as either a direct function (Bedford, Bailey, & Wilson, 1978; Mello, Lukas, Bree, & Mendelson, 1988; Roberts, Loh, & Vickers, 1989) or an inverted U-shaped function (Risner & Silcox, 1981; Roberts & Bennett, 1993). Again, compelling interpretations may be difficult to make, because differences in the shape of the functions may be due to param-

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eters of drug dose, ratio increment size, session length, and the operational definition of break point used.

Relative rate measures are also used to obtain data regarding the relation between drug dose and measures of responding or consumption. Relative rate measures express responding or consumption relative to a second measure of responding or consumption. For example, Lemaire and Meisch (1984, 1985) examined the joint effects of fixed-ratio (FR) response requirement and pentobarbital concentration. The data showed that across FR values, there was no simple relation between drug concentration and response rate. However, when drug deliveries obtained at a given FR value were expressed relative to drug deliveries obtained in a baseline condition (i.e., a low FR size, Lemaire & Meisch, 1984, 1985), a direct relation between drug concentration and percentage of baseline drug deliveries was observed. As FR value was increased, responding maintained by a larger drug concentration persisted at larger FR values than did responding maintained by the smaller drug concentrations. This result suggests that pentobarbital's reinforcing effects increased directly with concentration. This analysis is similar to that used with progressive-ratio methods; however, the dependent measure reported by Lemaire and Meisch is a relative measure, whereas break point under progressive-ratio schedules is an absolute measure.

Another relative rate measure is derived from choice procedures. Several studies have examined responding concurrently maintained by different doses of the same drug (Iglauer & Woods, 1974; Johanson & Schuster, 1975; Meisch & Stewart, 1995). Under these conditions, the larger drug dose maintained a greater proportion of responding relative to the lower dose. Related studies have examined responding maintained by concurrent access to drug reinforcers and alternative nondrug reinforcers (Carroll et al., 1991; Carroll, Rodefer, & Rawleigh, 1995; Macenski, Cutrell, & Meisch, 1993; Nader & Woolverton, 1991; Samson, Roehrs, & Tolliver, 1982). Often, variations in response requirement or magnitude of the alternative reinforcer are studied. The number of drug deliveries obtained consistently remains level or declines with either increases in response requirement or increases in magnitude of the

alternative reinforcer. It is important to note that, among studies that systematically varied either the response requirement or the alternative reinforcer magnitude and the reinforcer dose, the response rate decreases were relatively smaller for behavior maintained by higher drug doses (e.g., Carroll et al., 1991; Nader & Woolverton, 1991). A practical drawback of designs that use concurrent schedules is that, because the measure is relative, one cannot make statements about the absolute reinforcing effects of either one of the two options following an experimental manipulation. However, the findings summarized above are consistent with the statement that a drug's reinforcing effects increase directly with dose.

The current study systematically examined cocaine-maintained responding over a range of cocaine concentrations and FR values. A major goal was to investigate the relations among cocaine concentration, response rate, response requirement, persistence measures, and reinforcing effects. An additional aim was to compare the current findings with the other measures of reinforcing effects as outlined above. Demand-curve analysis describes consumption as a function of *unit price* using specific quantitative methods (Hursh, 1980; Hursh, Raslear, Shurtleff, Bauman, & Simmons, 1988). The current study also assessed the utility and accuracy of demand-curve analysis in relation to other dependent variables.

METHOD

Subjects

Six adult male rhesus monkeys (*Macaca mulatta*) served as subjects. The monkeys had a history of responding maintained by orally delivered ethanol and cocaine (Macenski & Meisch, 1992, 1995). The monkeys ranged in age from 10 to 14 years and weighed from 6.9 to 10.5 kg during the experiment. These weights were 80% to 90% of their ideal weights, as determined by veterinarians. Monkeys were individually housed in conventional primate cages, in a room maintained at 74 °F and illuminated from 7:00 a.m. to 7:00 p.m. Cages were arranged such that an individual monkey had visual, auditory, and olfactory contact with at least 4 other monkeys. They

were fed a daily ration of monkey chow and half an apple at 4:00 p.m. Except during the experimental session and three 1-hr periods starting at 10:00 a.m., 2:00 p.m., and 4:00 p.m., monkeys received 0.65 ml of water upon each contact with an active drinking spout. Availability of water was signaled by illumination of a green light above the water spout. Monkeys were cared for in accordance with rules established by the Committee on Care and Use of Laboratory Animal Resources, National Research Council (1985).

Apparatus

Experimental sessions were conducted in the monkeys' home cages (76 cm by 102 cm by 81 cm). Several holes were cut in one side of the cage such that a work panel could be attached from the outside, allowing the monkey access to experimental components. Work panels were composed of two liquid delivery systems, three stimulus lights, and a lever (not used in this study). Two covered 3-L stainless-steel liquid reservoirs were connected to the distal ends of a T-shaped bar on the back of each work panel. Polyethylene tubing (0.96 cm inside diameter) allowed liquid to flow from the reservoir to the rear of the liquid delivery system.

Each liquid delivery system (Kandota Instruments Inc.) consisted of a solenoid-operated valve and a brass spout. The brass spout acted as both the operadum for operant responses (mouth contacts) as well as the means to deliver solutions. Mouth contacts with the spout closed a circuit allowing response-dependent operation of control equipment located in another room. Based on previous experience with response topography and resulting response patterning, it was unlikely that monkeys were hand responding. Monkeys were occasionally monitored via closed circuit television, especially if response patterning was atypical of mouth responding; at no time were monkeys observed to use their hands to respond during experimental sessions. The brass spouts measured 1.2 cm outside diameter and 0.2 cm inside diameter and protruded 2 cm into the cage. The drinking systems were closed to avoid fluid loss by evaporation. The response topography and solenoid cut-off contingency functioned such that spillage was minimized. The delivery systems were centered within Plexi-

glas cups 9 cm in diameter. Four 1.1-W stimulus lights surrounded the spout and were fixed 2.8 cm from the spout. Lights located at 0° and 180° from vertical could be illuminated white, and those located at 90° and 270° could be illuminated green. A green light-emitting diode (2.5 cm diameter) was located 11.5 cm directly above each spout. The spatial arrangement of the components is described in Meisch, Henningfield, and Thompson (1975).

Programming of experimental conditions and data collection were accomplished with commercially available solid-state programming equipment (Coulbourn Instruments) located in an adjacent room. Graphic records of cumulative responses as a function of time were produced by cumulative recorders (Gerbrands). In addition, data transmission lines were connected to a PDP-11® computer (Digital Equipment) for the sole purpose of collecting number of drug and vehicle deliveries in 10-min bins.

Drug Preparation and Administration

A 1.0 mg/ml cocaine hydrochloride stock solution (National Institute of Drug Abuse) was mixed at least twice weekly and was stored in a refrigerator. Monkeys' daily cocaine solutions were mixed by adding a measured amount of stock solution to a volumetric flask and filling the remaining volume with tap water, which was the vehicle. Solutions were mixed at least 1 hr prior to the session and were left unrefrigerated until the session's start. Cocaine concentrations are expressed in terms of the salt.

Procedure

Monkeys previously had been trained to drink from the spouts, and their behavior had been maintained by orally delivered cocaine (Macenski & Meisch, 1995); thus, no manipulations were necessary to train responding. Experimental sessions were conducted 7 days per week from 11:00 a.m. to 2:00 p.m. During sessions, a cocaine solution and vehicle were available under a concurrent FR \times FR \times reinforcement schedule. The concurrent schedules were arranged such that responses or deliveries on one spout had no effect on the response requirement or reinforcer scheduling on the other spout. Session start was signaled by illumination of the

Table 1

Experimental condition sequence: Numbers refer to the order in which concentrations were studied.

FR size	Cocaine concentration (mg/ml)							
	0.8	0.57	0.4	0.2	0.1	0.05	0.025	0.0125
8	1, 9	2	3	4	5	6	7	8
16	10, 18	11	12	13	14	15	16	17
32	19, 27	20	21	22	23	24	25	26
64	28, 36	29	30	31	32	33	34	35
128	37, 40	38	39					
8	41, 49	42	43	44	45	46	47	48

Note. See the Appendix for information on conditions in which each individual monkey participated.

green stimulus light above each spout. Both stimulus lights blinked at a rate of 10 Hz for all monkeys except M-HP, for whom the light above the spout from which vehicle was available was illuminated constantly. During the session, contacts with the spout resulted in the illumination of the green spout lights for the duration of contact. To control for side preferences, the positions of the cocaine solution and vehicle were reversed each session.

Each monkey was studied under a condition until behavior became stable. The only exceptions were transitions from a low cocaine concentration to a redetermination at the highest concentration (see below). Stability was defined as six consecutive sessions with no increasing or decreasing trends in cocaine or vehicle deliveries. The total number of sessions each monkey spent under each condition is given in the Appendix.

Table 1 presents the basic order of experimental conditions for all monkeys. Briefly, monkeys initially responded under a concurrent FR 8 FR 8 schedule of 0.8 mg/ml cocaine and vehicle availability. A cocaine response curve was obtained using the following concentrations: 0.8, 0.57, 0.4, 0.2, 0.1, 0.05, 0.025, and 0.0125 mg/ml. Typically, cocaine concentration was reduced until there was overlap in 1 *SEM* of cocaine and vehicle means, or until the number of cocaine deliveries obtained was reduced by more than 75% of the previous value. The original condition, FR 8 (0.8 mg/ml cocaine), then was replicated. Conditions were not abruptly changed from the low concentration to the 0.8 mg/ml concentration; instead, each cocaine concentration was presented for 2 days in an ascending series. After

the replication, the FR value was doubled and another concentration response curve was obtained in a similar manner. Doubling the FR value typically continued until the number of 0.8 mg/ml cocaine deliveries obtained was reduced by more than 75% of the FR 8 value. A final cocaine concentration response curve was obtained under FR 8 as described above. Because the lowest cocaine concentration and largest FR value experienced by each monkey were based on an individual monkey's behavior, not all monkeys experienced all conditions indicated in Table 1. However, the order of conditions was the same for all monkeys. Conditions experienced by each monkey can be identified by examination of the Appendix.

A 1-hr timeout was in effect immediately preceding and following the session. During timeouts, responding had no scheduled consequences and all stimulus lights were extinguished. The timeout prior to the session was used to measure overnight water consumption, record data, fill reservoirs with measured amounts of cocaine and vehicle solutions, and flush tubing such that the first delivery would be of the correct solution. The timeout after the session was used to measure cocaine and vehicle consumption during the session, record data, fill a reservoir with water, and flush tubing of any remaining cocaine solution.

Data Analysis

In all cases, data are presented as the mean of the last six consecutive sessions. Thus, each mean value includes three values when drug was on the left side and three values when drug was on the right side. Cocaine was considered to be functioning as a reinforcer if 1 *SEM* of the cocaine and corresponding vehicle means did not overlap. With FR schedules, there is a direct relation between drug deliveries and response rate (i.e., drug deliveries per hour times FR value equals response rate). Thus, in figures that present number of drug deliveries as the dependent variable, statements may also be made regarding response rate.

Demand-curve analysis was completed on the data using the equation

$$\ln(Q) = \ln(L) + b(\ln P) - a(P), \quad (1)$$

where Q is consumption (milligrams of drug

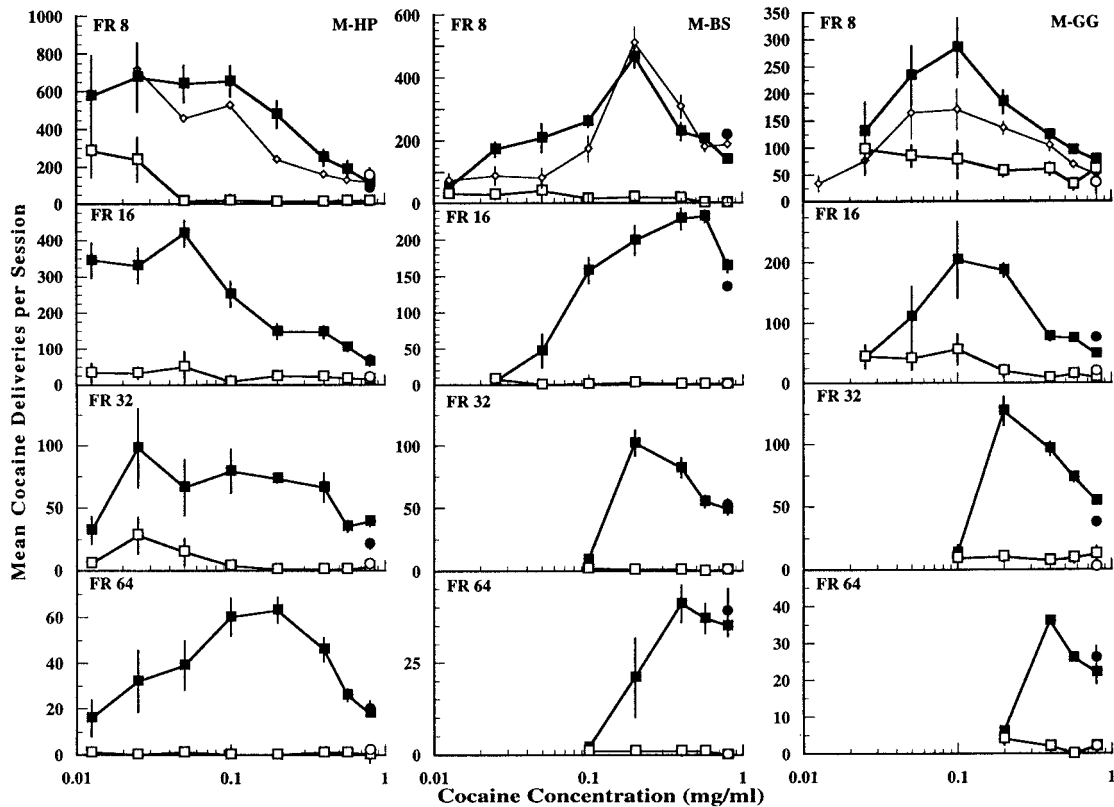


Fig. 1. Mean cocaine deliveries per 3-hr session are presented as a function of cocaine concentration across FR values for Monkeys M-HP, M-BS, and M-GG. Filled squares indicate cocaine deliveries. Open squares indicate deliveries of concurrently available vehicle. Circles indicate redeterminations. Small open diamonds indicate cocaine deliveries during the second dose-response curve determination at FR 8. Each data point represents a mean of the last six sessions in each condition, and error bars indicate 1 SEM. To reduce clutter, vehicle values for the FR 8 redetermination are omitted; typically these values were similar to the original determination. Note changes in ordinates across FR values.

per kilogram of body weight per session), P is unit price (responses per milligram cocaine per delivery), and L is the initial demand at low unit price, as found in Hursh (1991). Equations were derived by regressing $\ln(P)$ and P on the dependent variable $\ln(Q)$. Data were used for all points where there was no overlap in 1 SEM of the drug and corresponding vehicle values. Estimates for P_{\max} and point elasticities were also completed with the appropriate equations from Hursh (1991).

RESULTS

Figures 1 and 2 show that under FR 8, increases in cocaine concentration typically yielded increases and then decreases in cocaine deliveries per 3-hr session. For all mon-

keys under the initial FR 8 condition, the number of cocaine deliveries was substantially greater than the number of vehicle deliveries over a wide range of concentrations. As FR value was increased, the difference between cocaine deliveries and vehicle deliveries (i.e., there was no overlap in 1 SEM of the drug and corresponding vehicle values) was maintained at relatively larger cocaine concentrations but not at relatively smaller cocaine concentrations. Within sessions, when responding occurred, the rate was high. As FR value increased, pauses occurred intermittently after reinforcer delivery. Further, the majority of drug intake occurred immediately following the start of the session (data not shown).

For M-HP, M-BS, and M-GG, cocaine deliveries at larger cocaine concentrations exceed-

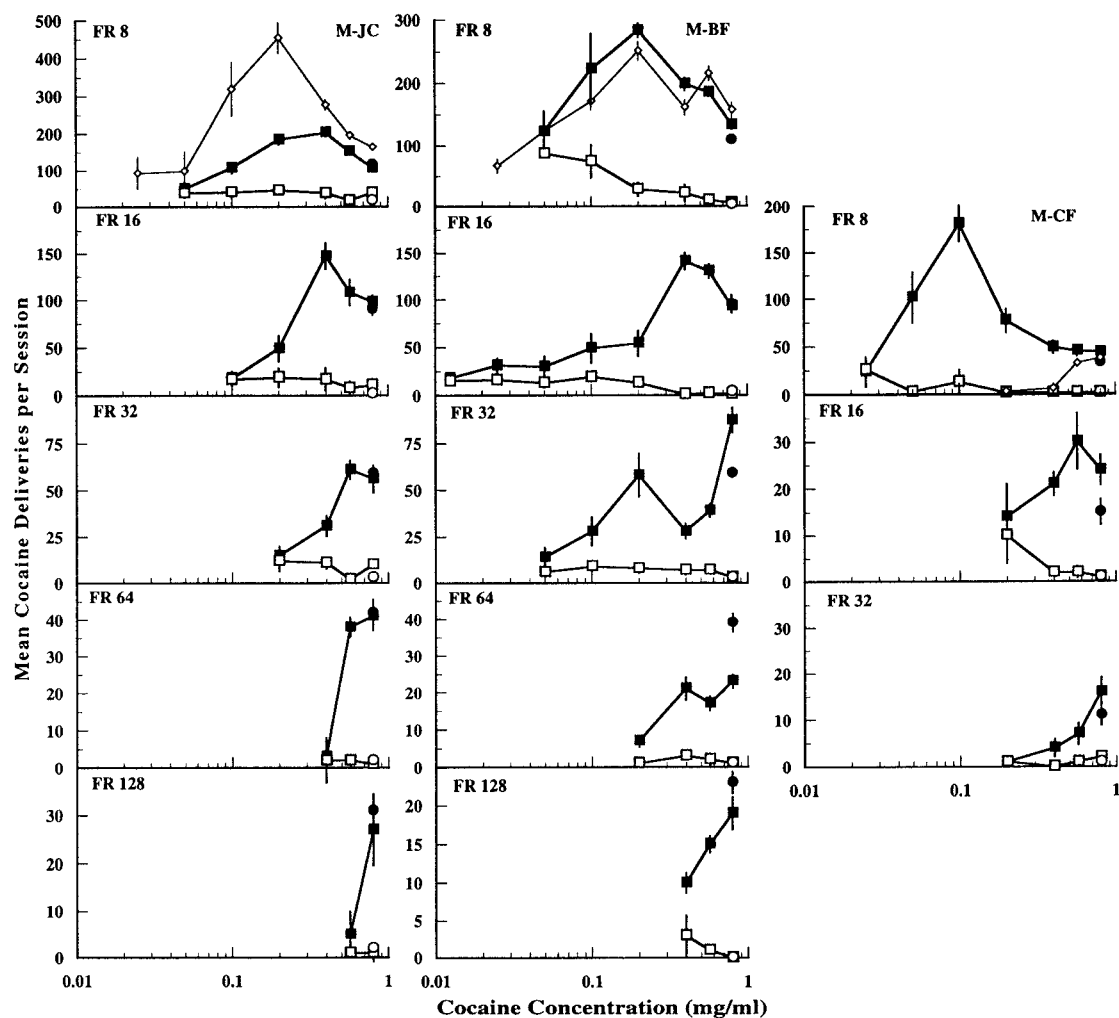


Fig. 2. Mean cocaine deliveries per 3-hr session are presented as a function of cocaine concentration across FR values for Monkeys M-JC, M-BF, and M-CF. See Figure 1 for details.

ed vehicle deliveries through a maximum FR size of 64 (see Figure 1). Deliveries and response rates of M-BS and M-GG were typically inverted U-shaped functions of cocaine concentration. Deliveries obtained by M-HP showed a characteristic descending limb on an inverted U-shaped function. For this monkey, the number of deliveries tended to show no changes at lower cocaine concentrations and relatively smaller FR values, but yielded a characteristic inverted U-shaped function at larger FR values. For these monkeys, a re-determination at FR 8 was similar to the original values, as were redeterminations of deliveries obtained at 0.8 mg/ml at all other FR values (data not shown).

Figure 2 shows that for M-JC and M-BF, the number of cocaine deliveries at the larger cocaine concentrations was greater than the number of vehicle deliveries through a maximum ratio value of 128, and it was greater for M-CF through a maximum ratio value of 32. At lower FR values the concentration response-rate function retained the characteristic inverted U-shaped features, but at higher FR values only the ascending limb of the function was produced. A second determination of deliveries obtained across concentration at FR 8 was similar to the original determination for M-BF (Figure 2). However, M-JC obtained substantially more cocaine deliveries, and M-CF received substantially fewer

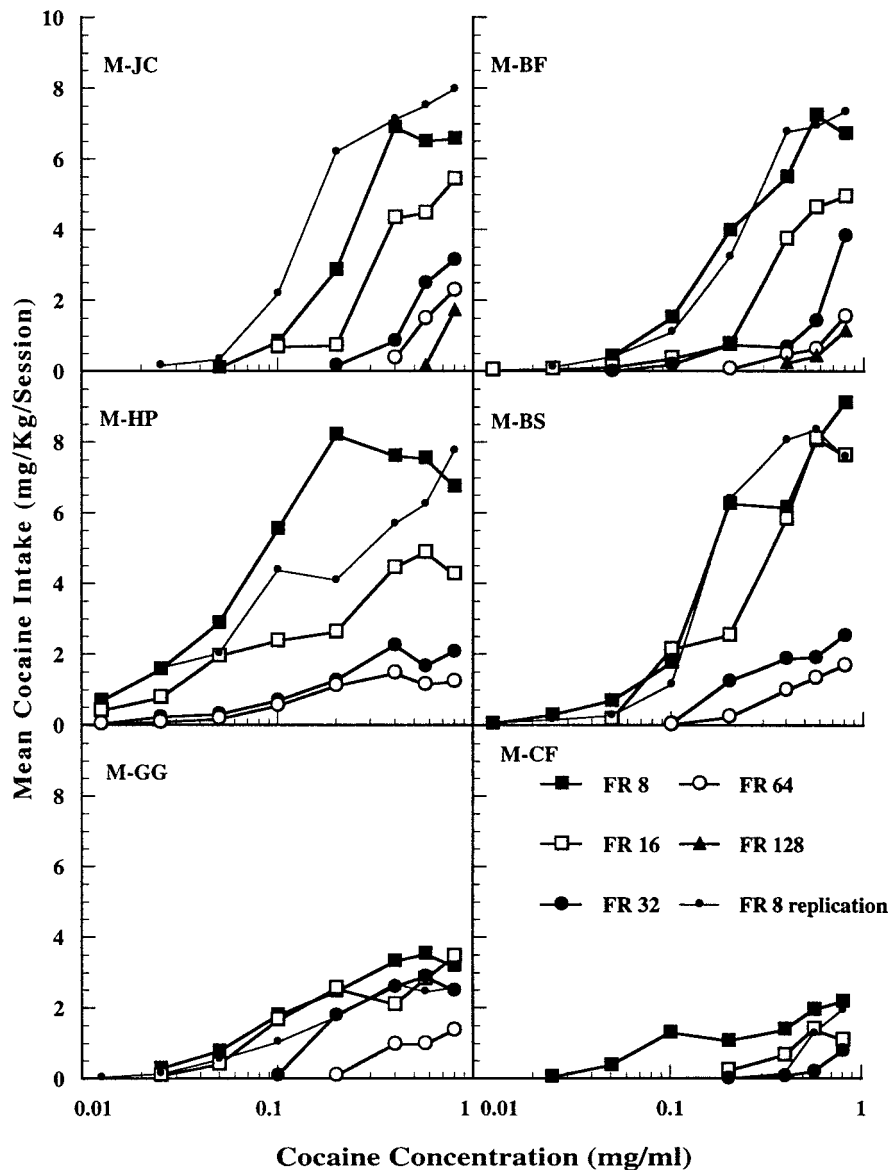


Fig. 3. Mean cocaine intake is presented for each of 6 monkeys as a function of cocaine concentration for several FR values. Each point represents the mean intake of the last six sessions in each condition.

deliveries. In the majority of cases, a second determination of the effects of 0.8 mg/ml cocaine (at all FR values) was similar to the original determination (data not shown).

Cocaine intake exceeded 8.0 mg/kg/session for M-BS (at 0.4, 0.57, and 0.8 mg/ml), M-JC (at 0.8 mg/ml), and M-HP (at 0.2 mg/ml). Figure 3 shows that cocaine intake (milligrams per kilogram per session) was a direct function of cocaine concentration and an in-

verse function of FR size for most monkeys. In a few cases, cocaine intake leveled off or declined slightly at the highest cocaine concentrations (e.g., M-HP).

Table 2 shows the cocaine concentration that maintained the highest response rate over all FR values tested and the smallest concentration for which there was no overlap in 1 SEM of the cocaine and vehicle means. Redetermination values were not considered in

Table 2

Cocaine concentrations (mg/ml) maintaining peak response rates and lowest concentrations (mg/ml) that were consumed in amounts greater than vehicle.

FR	Monkey					
	M-BF	M-CF	M-GG	M-JC	M-BS	M-HP
Concentration maintaining peak responding						
8	0.2	0.1	0.1	0.4	0.2	0.025
16	0.4	0.57	0.1	0.4	0.4	0.05
32	0.8	0.8	0.2	0.8	0.2	0.025
64	0.8		0.4	0.8	0.4	0.2
128	0.8			0.8		
Smallest reinforcing concentration						
8	0.05	0.05	0.05	0.1	0.025	0.025
16	0.1	0.4	0.1	0.2	0.05	0.0125
32	0.1	0.4	0.2	0.4	0.2	0.0125
64	0.2		0.4	0.57	0.2	0.0125
128	0.4					

Note. Smallest reinforcing concentration is defined as smallest cocaine concentration at which there was no overlap between 1 SEM of the cocaine values and 1 SEM of the vehicle value.

this evaluation, and not all monkeys were tested under all FR concentration combinations (see the Appendix). In general, the concentration at which the highest response rate occurred increased with increases in FR value. This was true for 4 of 6 monkeys. For M-HP, increases in FR were usually followed by increases in the concentration at which the highest response rate occurred. M-BS did not show a similar pattern. The smallest cocaine concentration yielding a clear separation between cocaine and vehicle deliveries increased as ratio value increased for all monkeys except M-HP.

In Figure 4, the percentage of cocaine deliveries relative to those obtained under FR 8 is presented as a function of cocaine concentration over several FR values. For each cocaine concentration, the percentage of deliveries under an FR 8 schedule was calculated by dividing the number of deliveries at each FR value by the number of deliveries at FR 8 and multiplying the result by 100%. There was a direct relation between proportion of deliveries obtained at FR 8 and cocaine concentration. Responding maintained by larger cocaine concentrations did not decline as much as responding maintained by smaller cocaine concentrations following increases in the response requirement. The most notable exception to this observation was M-GG,

whose curve at FR 16 exhibited a downward inflection at 0.4 mg/ml.

Figure 5 presents cocaine consumption as a function of cocaine unit price. Unit price was calculated by dividing the milligrams of cocaine in a single delivery at each concentration by the number of spout contacts required for delivery (see, e.g., Hursh, 1980). As cocaine's unit price increased, cocaine consumption decreased. Demand curves were fitted to the data for each monkey according to the equation given in Hursh (1991). The proportion of variance accounted for by unit price (r^2) ranged from 77% to 92% (Figure 5). Note that M-CF and M-JC had the lowest r^2 values and were also the monkeys that had noticeably different values at the original and redetermined FR 8 cocaine deliveries (Figure 1).

Figure 6 shows response rate, in number of responses per session, as a function of unit price. Overall, inverted U-shaped functions were obtained. Vertical lines represent P_{\max} and were calculated with the equation $P_{\max} = (1 + b)/a$. Parameters were obtained from the equations shown in Figure 5.

DISCUSSION

Oral Cocaine As a Reinforcer

Cocaine functioned as a reinforcer for the responding of all monkeys. This is evidenced by greater responding maintained by cocaine than by vehicle across a range of cocaine concentrations and FR sizes. The monkeys' responding followed the cocaine solution as its position was alternated with that of vehicle across sessions. Cocaine deliveries per session and thus cocaine-maintained spout contact rate under FR schedules in these fixed-duration sessions were orderly inverted U-shaped functions of cocaine concentration. This function is characteristic of drug-reinforced behavior in general (Macenski & Meisch, 1994; Young & Herling, 1986). The within-session response patterning was also typical of drug-reinforced responding under FR schedules. All of these results are consistent with cocaine's functioning as a reinforcer. These findings extend the range of conditions under which oral cocaine-reinforced behavior may be obtained (Macenski & Meisch, 1995; Meisch,

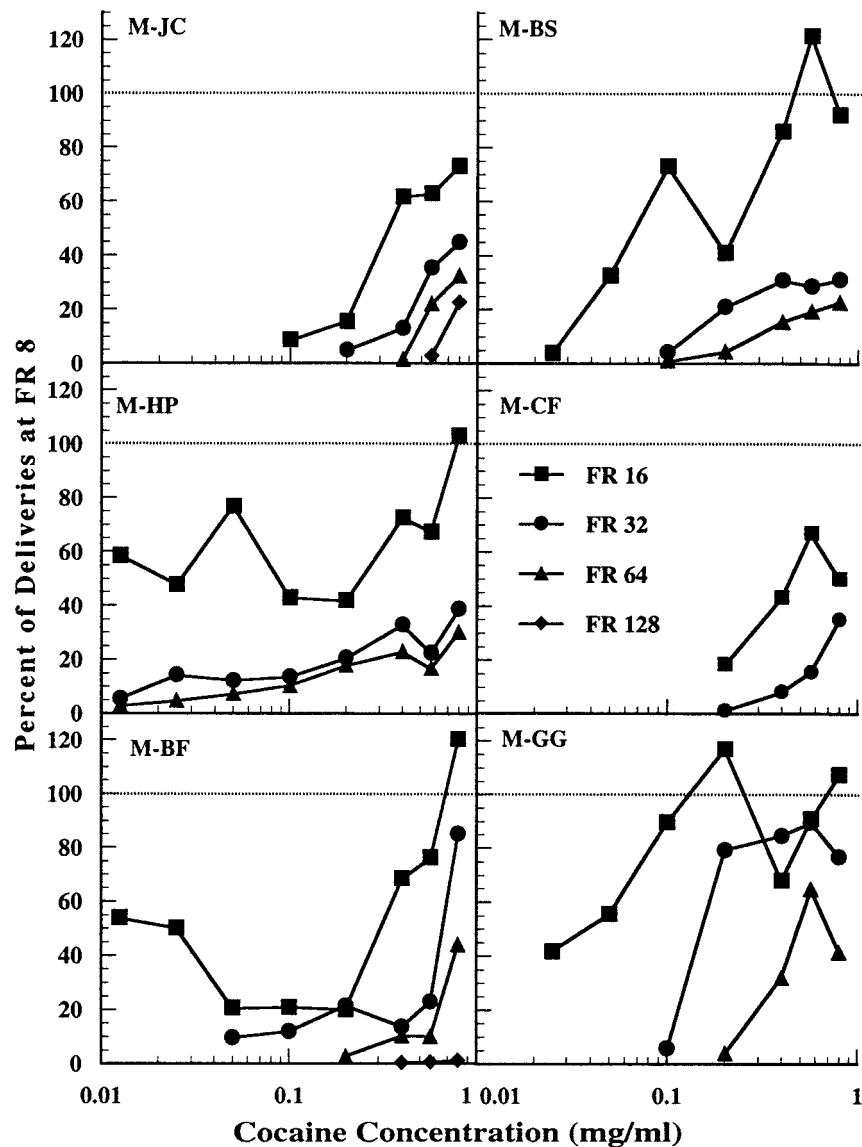


Fig. 4. The percentage of cocaine deliveries earned during 3-hr sessions at FR 8 is presented as a function of cocaine concentration across all FR values for each of 6 monkeys. Points were derived by dividing the mean number of cocaine deliveries at each dose and FR value by the mean number of cocaine deliveries at the appropriate cocaine concentration at FR 8.

Bell, & Lemaire, 1993; Meisch, George, & Lemaire, 1990) and are consistent with reports that cocaine will function as an orally delivered reinforcer in rodents (George, Elmer, Meisch, & Goldberg, 1991; Suzuki, Masukawa, Yoshii, Kawai, & Yanaura, 1990). These data also show that behavior maintained by orally delivered cocaine can be similar to that maintained by other admin-

istration routes (e.g., Goldberg, Morse, & Goldberg, 1976; Pickens & Thompson, 1968).

Cocaine consumption (in milligrams per kilogram per session) varied directly with cocaine concentration and inversely with FR value. These findings are consistent with previous studies of other drug reinforcers delivered orally (e.g., Ator & Griffiths, 1992;

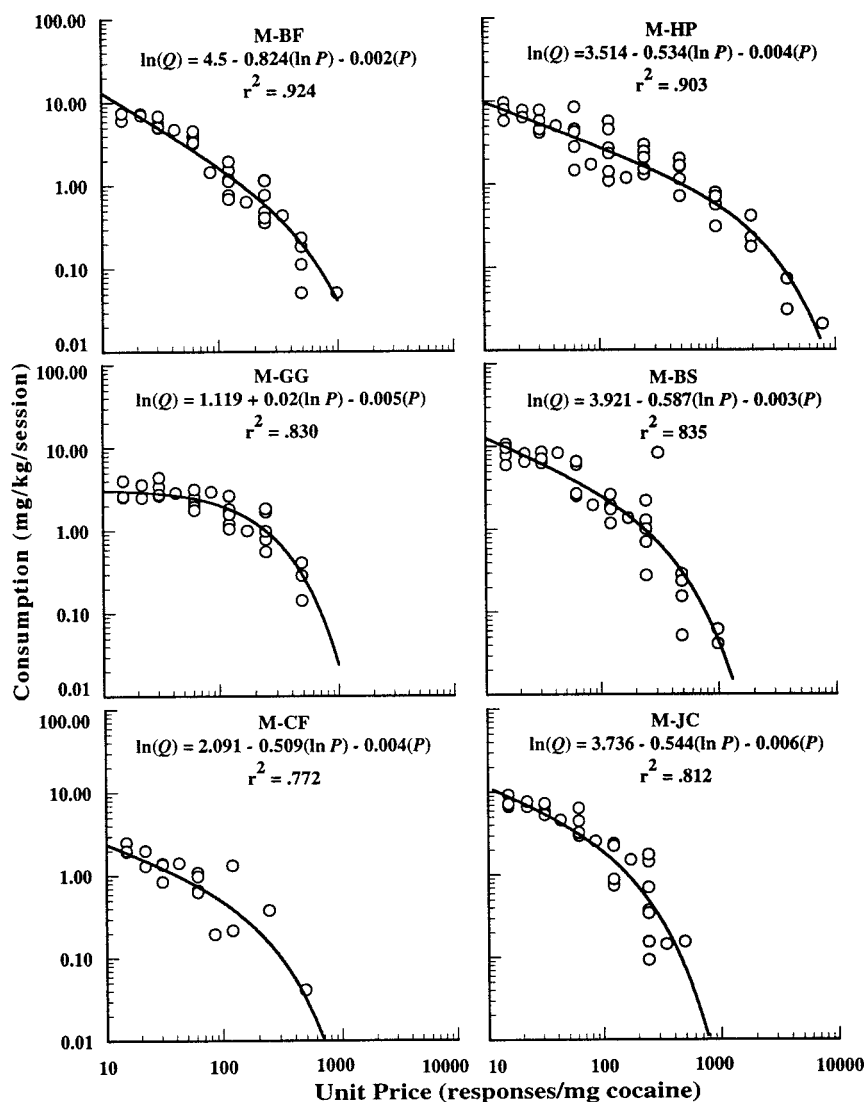


Fig. 5. Consumption of cocaine (in milligrams per kilogram per session) is presented as a function of unit price for individual animals. Each point represents the mean of the last six sessions at any particular unit price. Equations in each panel describe the fitted curve, and goodness of fit can be estimated by the r^2 parameter in each panel.

Carroll & Stotz, 1983; Lemaire & Meisch, 1984) and by other routes (e.g., Goldberg, 1973; Marquis, Webb, & Moreton, 1989; Pickens, Muchow, & DeNoble, 1981; Spear & Katz, 1991).

Relations Among Response Measures, Reinforcing Effects, and Concentration

There is general agreement that the ascending limb of the standard dose-response curve reflects increases in reinforcing effects (Katz, 1989; Skjoldager et al., 1991). However,

it is uncertain how to interpret the descending limb of the dose-response curve. We have argued that, other conditions being equal, reinforcing effects increase directly with dose and that changes in response rate do not always accurately reflect changes in reinforcing effects (Macenski & Meisch, 1994). Data obtained during this study show that the concentration that maintained peak response rates (Table 2) was dependent on schedule value. Therefore, there was no simple correspondence between response rate and drug

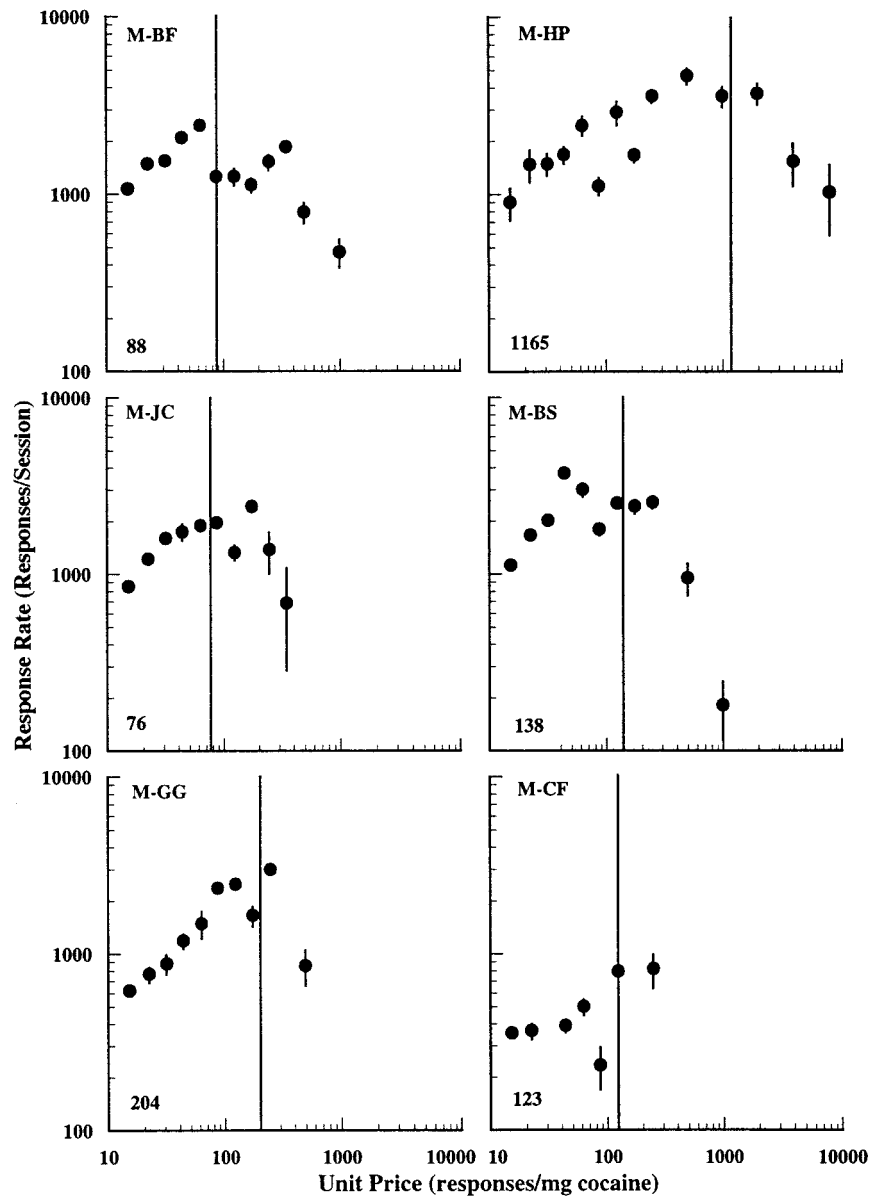


Fig. 6. Response rate in responses per 3-hr session is presented as a function of unit price. Each point represents the mean of the last six sessions at any particular unit price. Vertical lines represent P_{max} , and the exact P_{max} value is presented in the lower left of each monkey's panel.

concentration. Statements regarding the relation between reinforcing effects and response rate must be qualified by the schedule conditions under which they were obtained.

As FR value became larger, there were two changes. First, the concentration at which the highest response rate occurred increased. Second, the lowest concentration at which

drug-maintained response rate exceeded vehicle-maintained response rate also increased. The concentration-response curve shifted to the right with increases in FR value, suggesting that higher concentrations have greater reinforcing effectiveness. The current data are similar to those from previous studies of oral pentobarbital (a central nervous

system depressant) self-administration by rhesus monkeys. With pentobarbital, the concentration-response curves shifted to the right with increases in FR value (Lemaire & Meisch, 1984, 1985). With increases in FR value, right-shifted dose-response curves have been reported with intravenous drug self-administration by rhesus monkeys and rats, and across drug classes, showing generality across species and administration route (Marquis et al., 1989; Young & Herling, 1986).

The relation between response rate and reinforcing effects depends on schedule conditions. This finding has implications for research examining drug-maintained behavior. For example, in drug pretreatment studies, if a single dose of the pretreatment drug and a single dose of the reinforcing drug are used, the results will be uninterpretable with respect to changes in the drug's reinforcing actions. Increases and decreases in response rate can indicate either increases or decreases in reinforcing effects. This ambiguity stresses the need to collect data over a sufficient range of test conditions to permit interpretations regarding changes of a drug's reinforcing effects (Marquis et al., 1989; Mello & Negus, 1996).

The current results and interpretation of the present study are corroborated by progressive-ratio and choice studies. Break point under progressive-ratio contingencies is typically an inverted U or direct function of reinforcer magnitude (Mello et al., 1988; Roberts & Bennett, 1993). When an inverted U-shaped function was obtained, however, subsequent increases in the increment size yielded a direct function (Hodos & Kalman, 1963). Furthermore, in choice studies, the larger reinforcer was selected (Iglauer & Woods, 1974). These measures suggest that a drug's reinforcing effects increase directly with concentration.

Support for the assertion that relative reinforcing effects increase directly with dose can be found by examination of the percentages by which cocaine deliveries decreased as FR size increased. The highest cocaine concentrations show a proportionally smaller decline in deliveries obtained relative to the larger decline at lower cocaine concentrations. Thus, behavior maintained by larger concentrations was more persistent in that, at higher doses, response rate and cocaine de-

liveries showed relatively less decline compared with lower concentrations. When cocaine deliveries across concentrations were expressed as a ratio of deliveries obtained under FR 8, the resulting percentages tended to increase with the cocaine dose. The finding that the magnitude of decrease in drug responding and deliveries is inversely related to drug dose as FR value is increased has been reported in other drug self-administration studies with both oral and intravenous routes (Lemaire & Meisch, 1984, 1985; Marquis et al., 1989; see also Young & Herling, 1986).

The idea that the relative effectiveness of a reinforcer can be indexed by persistence in obtaining deliveries as FR value is increased is similar to Nevin's ideas regarding relative resistance of responding to change in his theoretical analysis of behavioral momentum. Nevin states that the strength of an operant can be indexed by examining behavioral momentum or the relative resistance to change of a steady-state behavior when challenged with a disrupting force (Nevin, 1974, 1992). Behavioral momentum research focuses on response rates within sessions, typically using pigeons responding under a food-maintained multiple schedule. The analysis focuses on changes in rate relative to a steady-state baseline. The current study and previous research by Meisch and colleagues have examined drug-maintained behavior of monkeys and rats following changes in either FR value or interreinforcer interval (Beardsley, Lemaire, & Meisch, 1993). The focus was on schedule completions or deliveries obtained as schedule parameters were changed across sessions. Typically, these studies employed rhesus monkeys or rats as subjects. An orderly relation between deliveries and reinforcer magnitude was observed when analyzed in terms of deliveries obtained relative to a steady-state baseline. Despite differences in experimental conditions, the concept of looking at data in relation to a steady-state baseline is the same across analysis methods and yields the same general outcome. That is, deliveries and schedule completions are more difficult to shift from a steady-state baseline if the reinforcing event is of greater rather than smaller magnitude. This assertion is important for several reasons. First, it suggests that despite many qualitative differences between drug reinforcers and more traditional reinforcers

such as food, both drug and food reinforcers (and possibly others) might produce the same functional relation between reinforcer magnitude and behavior under FR schedules (Kliner, Lemaire, & Meisch, 1988). Second, it suggests that, over a broad range of values, reinforcing effects increase directly with reinforcer magnitude. Third, it underscores the utility of using relative rate measures when making statements regarding reinforcing effects.

Demand-Curve Analysis

Behavioral economics offers another analysis of drug-reinforced behavior, which is comparable to persistence measures and behavioral momentum (Nevin, 1995). Demand-curve analysis relates consumption of a commodity to unit price, a ratio expressing response requirement to drug dose (Hursh et al., 1988). Because response requirement and drug dose are expressed as unit price, the specific relation between drug dose and reinforcing effects is superfluous. However, drug dose is a denominator term implying that larger doses have greater reinforcing effects. The current data are consistent with demand-curve analysis, in that maximum intake is found at the smallest FR values and at the largest cocaine concentrations. When combined into unit price, these variables would yield the lowest unit price and the greatest consumption. Thus, with schedule conditions equal, the larger unit dose would yield greater consumption.

P_{\max} is a constant derived from the demand-curve equation and is the unit price of highest response output. For P_{\max} to remain constant as FR value is increased, the drug concentration must also increase. Empirically, we have observed that the peak of the concentration-response curve shifts to the right with increases in FR value (i.e., to a larger cocaine concentration). Thus, predictions of the demand-curve equation have been empirically verified by data reported here.

The current data are described by the demand-curve function found in Hursh, (1991). In general, the variance in consumption was well accounted for by variation in unit price. r^2 ranged from .772 to .924, thus accounting for well over three quarters of the variance within individuals. These figures are consistent with those from a number of drug

self-administration studies in which data have been analyzed (or reanalyzed) using demand curves (Bickel, DeGrandpre, & Higgins, 1993, 1995; Bickel, DeGrandpre, Higgins, & Hughes, 1990). This analysis and others show that the demand-curve equation describes well the function between consumption and unit price. This appears to be true across species, drugs, and administration routes (Bickel et al., 1990, 1993; Bickel, DeGrandpre, Higgins, Hughes, & Badger, 1995; Carroll, 1993; Rodefer, DeRoche, Lynch, & Carroll, 1996; Spiga, Macenski, Meisch, & Roache, 1997; Winger, 1993; Winger, Woods, & Hursh, 1996). English, Rowlett, and Woolverton (1995) and Nader, Hedeker, and Woolverton (1993) have also shown that consumption decreases as price increases. However, Nader et al. (1993) used a linear equation that differed from the one proposed by Hursh et al. (1988), in that dose and FR were treated as separate main effects. The data presented by Nader et al. were better described using separate terms rather than the unit price equation. English et al. found no differences between a linear equation similar to the one used by Nader et al. and that proposed by Hursh et al. However, English et al. found that consumption was not equal at the same unit price.

Interestingly, despite the overall success of the demand curve in describing the relation between consumption and unit price, there are reports of a low-dose exception (Bickel et al., 1993; Van Etten, Higgins, & Bickel, 1995; Winger, 1993). The results of several studies showed that the demand curve did not predict consumption of a given unit price when composed of a small unit dose but did predict consumption of the same price unit when comprised of larger unit doses (Marquis et al., 1989; Van Etten et al., 1995). For example, a unit dose of 0.125 mg/kg cocaine, delivered intravenously, did not conform to unit price predictions (see Marquis et al., 1989, reanalyzed in Bickel et al., 1990). In contrast to the results of those studies, the current data show that consumption of orally delivered cocaine was well described by a demand curve at unit doses as low as 0.12 $\mu\text{g}/\text{kg}$ [see Figure 2, M-HP: (0.12 $\mu\text{g} \approx 0.0125 \text{ mg per ml cocaine} \times 0.65 \text{ ml per delivery})/7 \text{ kg}$]. The low dose in this study was over 100-fold lower than that in Marquis et al.

Bickel et al. (1993) have offered two explanations for the low-dose exception. One of these suggests that low doses are qualitatively different reinforcers that act "perhaps via conditioned reinforcement" (p. 178). Consistent with this possibility, we have argued that the taste of the drug solution becomes a conditioned reinforcer (and discriminative stimulus) in experienced animals (Macenski & Meisch, 1994). The fact that the low unit doses used in this study fell on the demand curve may be due to taste functioning as a conditioned reinforcer and thereby augmenting consumption. This argument is supported by results of other oral self-administration studies in which demand curves have fit the data well despite low unit doses (Lemaire & Meisch, 1984, 1985; Spiga et al., 1997). Common features among these studies include frequent oral delivery of small volumes; thus, the low-dose exception may be a function of experimental conditions.

Summary

Orally delivered cocaine can function as a reinforcer for rhesus monkeys, and substantial cocaine intake will occur. There was no simple correspondence between response rate and concentration. However, as the FR was increased, there was an orderly and direct relation between deliveries obtained, expressed as percentage of FR 8 baseline values, and drug concentration. The current data were well described by demand-curve analyses and thereby further support the utility of this metric. The findings described in this study support the conclusion that a drug's reinforcing effects increase directly with dose.

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APPENDIX

Number of days to stability for each monkey in each condition studied. See Table 1 for order in which conditions were studied.

Monkey	FR	Cocaine concentration (mg/ml)								
		0.0125	0.025	0.05	0.1	0.2	0.4	0.57	0.8	0.8R
M-GG	8			20	14	8	16	8	8	6
	16	8	10	10	8	11	8	8	8	7
	32			8	11	20	14	13	8	9
	64					18	8	14	12	8
	128						9	9	14	8
	8R		18	11	8	9	9	8	11	10
M-BS	8	26	9	11	8	11	12	8	8	16
	16		6	10	17	10	9	8	11	15
	32				11	8	12	8	21	9
	64				7	10	9	9	8	10
	8R	6	8	8	27	9	14	8	7	7
M-HP	8	11	9	10	9	8	11	8	25	19
	16	11	9	9	11	7	12	10	15	13
	32	15	8	11	9	8	8	8	9	10
	64	7	10	12	14	10	15	12	13	9
	8R		9	14	14	7	11	8	10	11
M-JC	8			8	10	9	8	8	8	7
	16				10	11	15	9	9	13
	32					8	12	15	11	10
	64						12	16	15	8
	128							8	8	15
	8R		8	20	8	9	10	9	8	7
M-CF	8		9	17	20	9	9	8	9	16
	16					8	12	11	9	8
	32					6	13	8	10	10
	8R					8	24	8	12	

Note. R = redetermination.